National PBM Drug Monograph
Technosphere Insulin Inhalation Powder (Afrezza)

VHA Pharmacy Benefits Management Strategic Healthcare Group
Medical Advisory Panel and VISN Pharmacist Executives

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

Efficacy	• Technosphere insulin (TI) is an orally inhaled rapid-acting insulin. There are two 24-week clinical trials that evaluated TI using the marketed device. Change in A1C was the primary outcome. • The addition of TI to basal insulin in patients with T1DM was found to be non-inferior to addition of aspart; however, the magnitude of change was less with TI (-0.21% vs. -0.4%) • TI was found to be superior to placebo when added to oral hypoglycemic agents in patients with T2DM (-0.82% vs. -0.42%)
Safety	• Cough was the most commonly reported adverse event occurring in 25-30% of patients in the TI groups. • TI causes a decline in FEV1 over time (treatment difference vs. comparators -40mL [95%CI -80, -1]). The decline was noted within the first 3 months of treatment and persisted over the duration of therapy. The annual rate of decline did not appear to worsen with continued use (up to 2 years of observation). • Lung cancer was reported with Exubera, another inhaled insulin. There were 4 cases of lung cancer reported with TI; 2 on therapy and 2 after completion of the trial. There were no cases reported in the comparator arms.
Other Considerations	• TI has a shorter duration of action than insulin aspart or regular insulin • TI is contraindicated in patients with chronic lung disease such as COPD or asthma • TI is not recommended in patients who smoke or who have recently stopped smoking • TI should not be used in patients with active lung cancer. Consider the risk versus benefits of using TI in patients with a prior history of lung cancer or in patients at risk for lung cancer. • Monitor pulmonary function at baseline and after 6 months of therapy and annually thereafter even in the absence of pulmonary symptoms. • There is less flexibility in dosing TI than injectable insulin. TI is dosed in 4U increments

Introduction

Afrezza is orally inhaled rapid-acting insulin that was approved in June 2014. It is a dry-powder formulation of insulin using Technosphere technology. Exubera, another dry-powder formulation was approved in 2006; however, it was removed from the market in 2007 because of poor acceptance by patients and providers. The device used to deliver Afrezza fits in the palm of the hand and is substantially smaller than the device used to deliver Exubera.

The preparation of Afrezza involves adsorption of regular human insulin onto Technosphere particles. The main component of the Technosphere is fumaryl diketopiperazine (FDKP), a proprietary excipient, which self-assembles into microparticles under acidic conditions. The insulin-containing particles are then freeze dried to form a dry powder. Once inhaled, the insulin-containing microparticles dissolve immediately at physiologic pH allowing insulin to be rapidly absorbed from the lung into the systemic circulation. It has been previously determined that the optimal size for particle delivery to the alveoli is 1-3µm in diameter. The median diameter of the Technosphere particles is approximately 2-2.5µm.

For the remainder of this review, Afrezza Technospehere insulin will be referred to as TI.

Pharmacokinetics/Pharmacodynamics

Insulin exposure is dose proportional with intrasubject variation of 34% for $AUC_{0\text{-}180min}$. Median time to peak concentration (Tmax) of TI is 12-15 minutes compared to approximately 120min with subcutaneously administered regular human insulin (RHI) and approximately 40 minutes with insulin lispro. Insulin concentrations returned to baseline by 180 minutes compared to >6 hours with RHI. However, the faster absorption with TI did not result in faster onset of activity compared to lispro.

FDKP Pharmacokinetics

FDKP is absorbed into the systemic circulation from the lungs. FDKP is not metabolized and is primarily renally eliminated. The negligible amount that is swallowed during inhalation is not absorbed. The Tmax of FDKP is approximately 10 minutes and has a half –life ranging from 114-198 minutes. There was no significant accumulation with typical dosing. The half-life was longer (270 minutes) in subjects with moderate renal impairment.

Subjects with COPD

In an open-label, single-dose (30 units) euglycemic glucose clamp study of non-diabetic subjects, TI pharmacokinetics were compared in those with a diagnosis of COPD (n=17) to those without COPD (n=19). TI was administered using the MedTone device. Individuals in the COPD group were required to have a post-bronchodilator FEV1/FVC ratio of <70%, prebronchodilator FEV1 ≥50% of predicted, total lung capacity ≥80% predicted, and uncorrected single-breath DL_{CO} ≥50% of predicted. Patients who currently smoked or who had stopped smoking within 6 months of the trial were excluded. There was no difference in insulin $AUC_{0\text{-}24h}$, peak concentration (Cmax) and Tmax for those with and without COPD.

Effect of smoking

Previous trials using other formulations of inhaled insulin found that absorption of inhaled insulin is increased in smokers compared to nonsmokers. (Becker 2006). In an open-label, single-dose euglycemic clamp study, the pharmacokinetics of TI 30 units was compared in patients with diabetes who smoke (n=12) to those who do not smoke (n=12). There was no significant difference in $AUC_{0\text{-}480min}$ and Cmax between smokers and non-smokers; however, median Tmax was significantly longer in smokers than non-smokers (20 versus 12 minutes respectively p=0.01).

FDA-Approved Indications

To improve glycemic control in adults with diabetes mellitus

Limitations of Use:

- TI is not a substitute for basal insulin; TI must be used in combination with long-acting insulin in patients with Type 1 diabetes
- Do not use for treatment of diabetic ketoacidosis
- TI is not recommended in patients who smoke or who have recently stopped smoking (e.g., less than 6 months)

Current VA Formulary Alternatives

Insulins: NPH, long-acting analogs, regular, aspart, premixed insulin
Oral medications: metformin, glipizide, saxagliptin, acarbose

How Supplied/Handling/Storage

TI is available in two strengths: 4 units (blue cartridges) and 8 units (green cartridges)

Each foil package comes with two blister cards. Each blister card contains 15 single-use cartridges. The blister card is perforated providing five strips with three cartridges per strip.

Table 1: How Supplied

4 unit cartridges	8 unit cartridges	Combination 4 and 8 unit cartridges
90 cartridges + 2 inhalers	90 cartridges + 2 inhalers	60-4 unit cartridges + 30-8 unit cartridges + 2 inhalers 30-4 unit cartridges + 60-8 unit cartridges + 2 inhalers 90-4 unit cartridges + 90-8 unit cartridges + 2 inhalers

The TI inhaler can be used for up to 15 days from date of first use; after 15 days of use, the inhale device should be discarded and replaced with a new inhaler device.

Not in Use (unopened):

- Sealed unopened foil packages stored in the refrigerator (36-42°F) may be used until the expiration date on the package.
- If an unopened sealed foil package is not refrigerated, TI must be used within 10 days

In Use (opened) Room Temperature Storage:

- Once a foil package has been opened and blister card removed, the unopened blister card must be used within 10 days
- Once a strip has been opened, the remaining doses must be used within 3 days

Dosage and Administration

Prior to initiating therapy with TI obtain medical history, physical exam, and spirometry to identify potential underlying lung disease. See Warnings and Precautions for recommended follow-up assessment of pulmonary function.

- Administer TI via oral inhalation at the beginning of the meal
- Cartridges should be at room temperature for at least 10 minutes before use
- Insulin naïve patients: Begin with 4 units of TI at each meal
- Patients using subcutaneous mealtime insulin: Use conversion chart shown in **Table 2**. Note that to attain certain doses, 4 and 8 unit cartridges may need to be combined. For example, a patient requiring 12 units will need to use one 4 unit plus one 8 unit cartridge.
- Dosage adjustment is based on blood glucose monitoring results and patient's glycemic goal
- Provide patient with instructions for proper use (see package insert for detailed instructions)

Table 2: Mealtime TI Dose Conversion Table

Injected mealtime insulin dose	TI Dose	Number (n) of cartridges Needed
Up to 4 units	4 units	(1) 4 unit cartridge
5-8 units	8 units	(1) 8 unit cartridge
9-12 units	12 units	(1) 4 unit cartridge + (1) 8 unit cartridge
13-16 units	16 units	(2) 8 unit cartridges
17-20 units	20 units	(1) 4 unit cartridge + (2) 8 unit cartridges
21-24 units	24 units	(3) 8 unit cartridges

Efficacy

The original NDA submission utilized a delivery system (MedTone) for TI that was not marketed. The FDA reviewers noted that issues with trial methodology may have confounded interpretability of the results. The FDA issued a Complete Response letter in 2010 noting deficiencies in efficacy, safety, and inhaler device-related issues. The sponsor informed the FDA that it was going to abandon the MedTone device in lieu of a new device, the Gen-2 inhaler. The sponsor submitted *in-vitro* performance data of the new device and a single dose PK study comparing the old and new devices. The FDA issued a second Complete Response letter in 2011 indicating that the data submitted were not sufficient to support approval. The FDA requested that at least 2 clinical trials using the Gen-2 inhaler be conducted and that at least 1 study include arms directly comparing the MedTone and Gen-2 devices. In addition, they asked that the trials be designed to resolve the some of the deficiencies noted in the earlier trials using the MedTone device. Results of the clinical trials using the MedTone device are provided in **Table 3** for historical purposes.

Table 3: Studies using MedTone Device

	Design	Type Diabetes	Duration	Patients	Treatment arms	Baseline A1C (%)	Δ A1C (%)	Final insulin dose (units)
Study 005	R, DB, PC	Type 2	11 weeks	Add-on to glargine All patients started with 14units TI and force-titrated on a weekly basis (14unit intervals) to final dose	TI 14units (n=43) TI 28units (n=43) TI42units (n=41) TI 56units (n=42) PBO (n=41)	8.9 8.6 8.7 8.8 8.7	-0.3 -0.6 -0.5 -0.6 0.2	NA
Study 0008 Rosenstock 2008	R, DB, PC	Type 2	12 weeks	Add-on to ≥1 OAD	TI (n=61) PBO (n=62)	7.9 7.8	-0.7* -0.3	TI 30
Study 014	R, OL	Type 2	24 weeks	Add-on to glargine	TI (n=150) Aspart (n=155)	8.9 9.0	-0.9 -1.3*	TI 135/GLA 40 Asp 24/GLA 34
Study 102 Rosenstock 2010	R, OL	Type 2	52 weeks	MET, TZDs may be continued	TI + glargine HS (n=302) BiAsp insulin BID (n=316)	8.7 8.7	-0.6 -0.7	TI 198/GLA 47 BiAsp 88
Study 103	R, OL	Type 2	12 weeks	Pts. were previously taking MET+SU	TI alone (n=176) TI+MET (n=169) SU+MET (n=162)	8.9 9.0 8.9	0.2 -0.7 -0.8	TI 240 TI+MET 190 N/A
Study 101	R, OL	Type 1	12 weeks	Add-on to glargine	TI (n=51) Aspart (n=56)	9.0 8.9	-0.8 -1.0	TI?/GLA? Asp 20/GLA 22
Study 009	R, OL	Type 1	52 weeks	Add-on to glargine	TI (n=277) Aspart (n=262)	8.4 8.5	-0.1 -0.4*	TI 150/GLA 33 Asp 31/GLA 30

Studies 005 and 0008 used different delivery system for Afrezza
Abbreviations: BiAsp=insulin aspart 70/30; DB=double-blind; GLA=glargine; MET=metformin; NA=not applicable; OAD=oral antidiabetic drugs; PBO=placebo; PC=placebo-controlled; R=randomized; SU=sulfonylurea; TI=technosphere insulin; TZDs=thiazolidinediones

The 2 FDA-required studies using Gen-2 device are shown in **Table 5**. For detailed information, refer to **Appendices 1 and 2**. The T1DM study compared TI using the earlier device and the marketed device and insulin aspart as add-on to the patient's current basal insulin. The T2DM study compared TI to inhaled placebo as add-on to metformin alone or ≥ 2 oral agents. Both trials were 24 weeks in duration, with the first 12 weeks for optimizing the prandial insulin dose and the second 12 weeks as the stable dose phase.

Dosing for T1DM trial

Patients remained on their usual basal insulin. At the end of the 4-week basal optimization phase, patients were required to have a FBG ≤180mg/dL. The approximate conversion of TI to injectable insulin was as follows (note that the conversion for Gen-2 does not correspond with the marketed dosing strengths). For example, patients who had been receiving 0-4 units of injectable prandial insulin were converted to 10 units of TI Gen-2, 4-8 units of injectable converted to 20 units of TI Gen-2 and so on.

- TI Gen-2: 10units TI ~ 4units aspart
- TI MedTone: 15units TI ~ 4units aspart

During the first 12-weeks, the dose of insulin was titrated according to an algorithm based on the median value of the 3 most recent measurements for each meal. Titration for TI was based on 90-minute post-prandial BG values; titration for aspart was based on pre-meal BG of the next meal.

Table 4: TI and Insulin Aspart Dosing Adjustments

Median 90 min PPG (mg/dL)	TI Gen-2 dose adjustment	Median pre-next meal BG level (mg/dL)**	Insulin aspart adjustment
<110	Decrease by 10 units	<100	Decrease by10%
≥110 to <160	Maintain current dose	≥100 to <120	Maintain current dose
≥160	Increase by 10 units at the same meal	≥120 to <140	Increase by 1unit
NA	NA	≥140 to <180	Increase by 2units
NA	NA	>180	Increase by 3units (or 10% of dose)

**Based on at least 3 measurements on 3 separate days
NA=not applicable

If the 90-minute PPG was ≥ 180mg/dL, a supplemental post-meal dose of TI Gen-2 10units (15units for TI MedTone) was allowed. Those who developed ≥ 2 episodes of hypoglycemia were instructed not to take additional supplemental doses and to contact the investigator. For those with 90-minute postprandial

glucose (PPG) levels ≥110 to <160mg/dL for a given meal, but had 2 out of 3 pre-prandial blood glucose ≥160mg/dL for that meal, a supplemental dose of TI was to be administered on a scheduled basis 90 minutes after the start of that meal. The mealtime dose could be reduced at the discretion of the provider.

During the stable dose phase, those who had 90-minute PPG ≥180mg/dL, supplemental insulin of TI 10units was allowed at the time of the PPG reading.

The maximum total daily dose allowed for TI Gen-2 was 4units/kg and TI MedTone was 6units/kg.

Dosing for T2DM trial
All patients randomized to TI were started with TI 10units or placebo with each meal. Dosage titration was the same as described in **Table 4**. Patients remained on their pre-study oral agents and doses could not be altered without discussion between the primary investigator and sponsor.

For those who reached a dose of at least 30units for a given meal and who no longer saw a ≥10mg/dL decrease in the corresponding median 90-minute PPG value, despite 3 subsequent 10unit dose increases (above 30units) were to stop further mealtime dose increases and to contact the investigator.

For those with persistently elevated pre-meal blood glucose of >130mg/dL, post-meal supplementation on a scheduled basis was allowed.

Open-label rescue therapy was provided for those who met pre-specified criteria. For those who entered the trial with metformin monotherapy, glimepiride was used as rescue; for those entering with ≥2 oral antidiabetic agents (OADs), insulin glargine was used as rescue.

Results
The addition of TI to basal insulin in patients with T1DM was found to be non-inferior to addition of aspart; however, improvement in A1C was numerically less with TI than aspart. TI was found to be superior to placebo when added to OADs in patients with T2DM (**Table 5).**

In the T1DM study, the mean change in basal insulin dose from baseline to week 24 was 4units and 1unit for TI Gen-2 and aspart respectively. The mean change in prandial insulin dose from week 1 to week 24 was 30.7units and 1.6units respectively. It appears that a higher mean basal insulin dosage and greater prandial insulin titration was needed in the TI group despite less improvement in A1C relative to aspart.

The mean daily insulin dose in the T2DM study was 92.3units and 128units for TI and placebo respectively. Rescue treatment was required in 6.8% of those in the TI group and 9.7% in the placebo group. Need for supplemental insulin was not described in either of the trials.

Table 5: Glycemic Efficacy using Gen-2 Device (24-week Trials)

Design	Type Diabetes	Treatment arms	Baseline A1C (%)	Δ A1C (%)	A1C≤7% (%)	Baseline FPG (mg/dL)	FPG (mg/dL)	Final insulin dose prandial/basal (units)
Study 171 R, DB	Type 1	TI Gen-2 + basal insulin (n=174)	8.0	-0.21	18.3	154	-25.3	115.4/32
		Aspart + basal insulin (n=170)	7.9	-0.4	30.7	152	10.2	25.9/26
Study 175 R, DB, PC	Type 2	TI Gen-2 + OAD (n=177)	8.3	-0.82	32.2	176	-11.2	92.3/NA
		PBO + OAD (n=176)	8.4	-0.42	15.3	175	-3.8	128/NA

Abbreviations: DB=double-blind; FPG=fasting plasma glucose; NA=not applicable; OAD=oral antidiabetic drugs; PBO=placebo; PC=placebo-controlled; R=randomized

Long-term studies
The FDA is requiring a five year post-marketing randomized, controlled trial (n=8000-10,000) comparing TI to standard of care in patients with type 2 diabetes. The primary objective is to evaluate the potential risk for pulmonary malignancy. This trial will also assess cardiovascular risk and long-term effect on pulmonary function.

Quality of Life/Treatment Satisfaction
There are no published quality of life studies using TI Gen-2. Patient-reported outcomes were assessed in the 52-week study using the MedTone device. Patients with T2DM randomized to TI + glargine or

premixed aspart 70/30 completed the SF-36 measuring quality of life and the Inhaled Insulin Treatment Questionnaire which measures treatment satisfaction before and after treatment. There were no between-treatment differences in change for any of the measures.

Adverse Events (Safety Data)

The pooled safety data includes those trials in the original NDA submission and the newer trials. There were a total of 3017 patients exposed to TI (2647 using MedTone; 370 using Gen-2), 290 to placebo, and 2198 to comparators. Duration of exposure to TI was 0-3 months (n=896), >3 to 6 months (n=978), >6 to 12 months (n=419), and >12 months (n=724). Nearly twice as many patients withT2DM (n=1991) than T1DM (n=1026) were enrolled.

Deaths

There was 10/3017 (0.33%) deaths in the TI group and 7/2198 (0.32%) in the comparator group. The exposure-adjusted rates were 0.44 and 0.33 per 100 patient-years for TI and comparators respectively. According to the FDA reviewers, the deaths did not appear to be directly related to treatment. The majority of deaths were due to cardiovascular causes.

Specifically in Gen-2 trials 171 and 175, there was one death in the insulin aspart group and none in any of the TI groups or placebo group.

Serious Adverse Events (SAEs)

The combined incidence for Gen-2 and MedTone, showed fewer SAEs with TI versus comparator (7.1% vs. 8.6%); however, there were more SAEs with TI than TI placebo (7.1 vs. 3.8). The majority of SAEs for the active TI groups were with the MedTone device. Considering the Gen-2 studies only, there were fewer SAEs with TI Gen-2 compared to TI Gen-2 placebo or comparator (**Table 6**). There was a wide range of SAEs reported using the MedDRA System Organ Class. There was no specific pattern of SAEs; however, many, for all treatment arms, in the T2DM trial were cardiovascular-related as would be expected in this population.

Table 6: Serious Adverse Events (Pooled Safety Data)

	N	Patient-years exposure	Any treatment -emergent SAE (%)
TI (active drug)			
Gen-2	370	149	3.0
MedTone	2647	1903	7.6
Total	3017	2052	7.1
TI placebo*			
Gen-2	176	73	5.1
MedTone	114	25	1.8
Total	290	98	3.8
Comparators	2198	2152	8.6

Data obtained from FDA briefing documents
*Carrier particle without insulin used as placebo

Common Adverse Events

The most common treatment-emergent adverse events were hypoglycemia, cough and upper respiratory tract infection. Cough occurred in approximately 27% of patients receiving TI and was characterized as mild; 2.8% of TI treated patients discontinued therapy due to cough. Cough occurred within 10 minutes of inhalation and the frequency diminished over time with continued use.

Table 7: Adverse Events Occurring in ≥2% of Patients and More Often with TI than Comparator

	Type 2 Diabetes			Type 1 Diabetes	
	TI (n=1991)	Non-placebo comparators (n=1363)	Placebo (n=290)*	TI (n=1026)	Subcutaneous insulin (n=835)
Cough	25.6	5.4	19.7	29.4	4.9
Throat pain or irritation	4.4	0.9	3.8	5.5	1.9
Headache	3.1	1.8	2.8	4.7	2.8
Diarrhea	2.7	2.2	1.4	-	-
Productive cough	2.2	0.9	1.0	-	-
Fatigue	2.0	0.6	0.7	-	-
Nausea	2.0	1.0	0.3	-	-
Decreased pulmonary function	-	-	-	2.8	1.0
Bronchitis	-	-	-	2.5	2.0
Urinary tract infection	-	-	-	2.3	1.9

*Carrier particle without insulin used as placebo
Data obtained from product package insert
Hypoglycemia is excluded from this table and discussed separately

Other Adverse Events

Hypoglycemia

Mild-moderate hypoglycemia was defined as self-monitored blood glucose levels <70mg/dL and/or symptoms of hypoglycemia relieved by self-administration of carbohydrates. Severe hypoglycemia was defined as any event requiring (not requested by the patient) assistance of another person to actively administer carbohydrate or glucagon.

The incidence and event rates for hypoglycemia in the T1DM study were lower with TI-treated patients than insulin aspart (**Table 8**). This may be because mean reduction in A1C was less with TI than aspart. In the T2DM study, there was a higher rate of events in the TI vs. the placebo group.

Table 8: Hypoglycemia

	T1DM (Study 171)			T2DM (Study 175)	
	TI Gen-2 (n=174)	TI MedTone (n=173)	Aspart (n=171)	TI Gen-2 (n=177)	Placebo (n=176)
All					
n (%)	167(96)	166(96)	170 (99.4)	120 (67.8)	54 (30.7)
Event rate **(per pt-mo)**	9.8	10.3	13.97	1.16	0.5
Mild-moderate					
n (%)	166 (95.4)	166 (96)	170 (99.4)	NA	NA
Event rate **(per pt-mo)**	9.72	10.2	13.83		
Severe					
n (%)	32 (18.4)	37 (21.4)	50 (29.2)	9 (5.1)	3 (1.7)
Event rate **(per 100 pt-mo)**	8.05	9.99	14.45	2.37	0.6
BG ≤36mg/dL					
n (%)	41 (23.6)	45 (26)	63 (36.8)	3 (1.7)	2 (1.1)
Event rate **(per 100 pt-mo)**	11.64	13.05	25.57	0.68	0.24

Data obtained from FDA Briefing Documents

Lung Cancer

Lung cancer was reported with Exubera. In clinical trials with TI, lung cancer (2 cases in 2750 patient-years of exposure) was reported in the TI group versus none in the comparators (0 cases in 2169 patient-years of exposure). Both patients had a prior history of heavy tobacco use (40 pack-years and 54 pack-years). Two additional cases of lung cancer (both squamous non-small cell) occurred in non-smokers exposed to TI and were reported after trial completion.

Table 9: Lung Cancer Cases

	Age	Sex	DM Type	TI Exposure	Diagnosis Time	Histology
Clinical trial	61	M	T2DM	137 days	137 days	Neuro-endocrine oat cell (small cell)
Clinical trial	66	M	T2DM	627 days	627 days	Bronchogenic cancer non-differentiated NSCLC, T4 N2 M0
Post-trial	59	M	T2DM	3.5 years	2.5 years	Squamous NSCLC
Post-trial	73	F	T2DM	1 year, 11 months	3.5 years	Squamous NSCLC, Stage II

NSCLC=non-small cell lung cancer

Pulmonary Function

Like other organs, the lung may be a target for complications resulting from diabetes. In patients with diabetes, the rate of decline in pulmonary function has been found to be faster than in non-diabetic, non-smoking subjects.

Pulmonary function tests (PFTs) were assessed as an adverse event of special interest. The PFT safety population was based on pooled results of trials with treatment duration of at least 12 months. Data were pooled from trials 009, Rosenstock (2010), and the two year pulmonary function study by Raskin et al. The patient population included both T1DM and T2DM patients. Although the MedTone device was used in these trials, direct comparison of TI delivered via the Gen-2 and MedTone device (Study 171), found that the change in FEV1 at 6 months was similar between devices and to the findings in the original NDA submission (-0.07L and -0.08L for Gen-2 and MedTone respectively).

Patients with underlying lung disease (e.g., COPD, asthma), current or former smokers (within 6 months) and history of malignancy within 5 years, or abnormal lung function were excluded from the trials. The 2-year open-label study was specifically designed to evaluate pulmonary function. Patients with T1DM or T2DM were randomized to TI or usual care. The majority of patients had T2DM (71%). The average A1C was 8.7%, duration of diabetes 11.8 years, and 30% were past smokers.

Pulmonary function measurement at month 3 indicates decline in FEV1 occurs early after initiating TI and does not progress over a two year treatment period (**Table 10**). Mean changes in PFTs were similar in patients with T1DM and T2DM and were not associated with insulin dose.

Table 10: Change from Baseline in FEV1 (L) Pooled Results

Month 3	Month 6	Month 9	Month 12	Month 18	Month 24
-0.040	-0.043	-0.036	-0.038	-0.045	-0.045
[-0.056, -0.025]	[-0.059, -0.028]	[-0.056, -0.016]	[-0.055, -0.020]	[-0.065, -0.025]	[-0.069, -0.022]

Results shown as difference between treatment groups (TI – Comparator)
Mean change [95%CI]
Data obtained from the FDA Afrezza Briefing Document Mannkind Corp

In the pooled population, 21.7% and 23.2% of those randomized to TI and comparator respectively had a ≥15% decrease from baseline in PFTs (FEV1, FVC, TLC, DLco) at some point during the trials.

An unpublished study (trial 126) of patients with type 1or 2 diabetes who were treated from 6 months to 2 years, found that the changes in PFTs resolved one month after discontinuing TI

Weight

In the T1DM trial, change in weight was more favorable in the TI versus the aspart group. In the T2DM trial, the mean weight gain observed with TI was approximately 0.5kg compared to mean weight loss of 1.1kg in the placebo group (**Table 11**).

Table 11: Weight

	Treatment Arms	Mean Prandial/Basal Insulin Dose (units)	Baseline Weight (kg)	Weight (kg)
Study 171	TI Gen-2 + basal insulin	115.4/32	75.7	-0.39
	TI MedTone + basal insulin	137.7/not shown	76.8	Not shown
	Aspart + basal insulin	25.9/26	72.6	0.93
Study 175	TI Gen-2 + OAD	92.3/-	90.2	0.49
	PBO + OAD	128/-	90.8	-1.13

Cardiovascular
Based on a pooled analysis of 9 phase 2/3 studies (n=4467) of TI and usual care, the incidence of cardiovascular or cerebrovascular events (events not adjudicated) was similar RR=1.01 [95%CI 0.84, 1.20].

Table 12: Risk of Cardiovascular Events

	TI events (n)	Comparator events (n)	RR [95%CI]
All diabetes	198	171	1.01 [0.84, 1.20]
Type 2 diabetes	167	136	1.02 [0.84, 1.24]
Type 1 diabetes	31	35	0.85 [0.55, 1.30]

Diabetic Ketoacidosis in Patients with T1DM
In the type 1 diabetes clinical trials, DKA was more commonly reported in the TI group (n=13; 0.43%) than in the comparator groups (n=3; 0.14%). The exposure adjusted rates were 2.4 and 0.4 per100 patient-years for TI and comparators respectively.

Insulin Antibodies
Increase in anti-insulin antibodies were observed in patients receiving TI than injectable mealtime insulin. Presence of antibodies did not correlate with decreased efficacy or increased risk of adverse reactions.

Tolerability
The discontinuation rates due to adverse events in the T1DM trial (171) were 9.2%, 5.2% and 0% in the TI Gen-2, TI MedTone, and aspart groups respectively. In the T2DM trial (175), 4% in the TI Gen-2 group and 5.1% in the placebo group discontinued treatment due to an adverse event.

The pooled discontinuations rates from the Gen-2 and MedTone trials due to AEs for the T1DM studies were 6.6% for TI and 0.5% for comparator. The pooled rates for the T2DM studies were 7.5% for TI, 3.4% for placebo TI, and 1.5% for comparator. Pulmonary-related AEs including cough were more common in TI-treated patients and accounts for much of the difference in dropout rates between TI and non-TI groups.

Contraindications
- Patients with chronic lung disease such as COPD or asthma
- Hypersensitivity to regular human insulin or any of the TI excipients
- Use during episodes of hypoglycemia

Warnings and Precautions
Acute bronchospasm in patients with chronic lung disease: Prior to initiating therapy with TI obtain medical history, physical exam, and spirometry to identify potential underlying lung disease. Bronchoconstriction and wheezing occurred in 5 out of 7 (29%) of patients with asthma compared to 0 out of 13 patients without asthma. In the patients with asthma, mean FEV1 decreased by 400mL 15 minutes after a single dose. In a study of 8 patients with COPD, mean FEV1 decreased by 200mL 18 minutes after a single dose.

Decline in pulmonary function: Clinical trial data lasting up to two years in patients without chronic lung disease shows that TI causes a decline in FEV1 over time. The decrease in FEV1 (40mL [95%CI -80, -1]) was greater in TI treated patients than comparators. The decline was noted within the first three months of treatment and persisted over the duration of therapy. The annual rate of decline did not appear to worsen with continued use (up to two years of observation). The effect of TI on pulmonary function beyond two years of use or reversal of effect on FEV1 after discontinuation of TI is unknown.

Monitoring of pulmonary function: Baseline and after six months of therapy and annually thereafter even in the absence of pulmonary symptoms. Consider discontinuing TI in patients who have a ≥20% decline in FEV1 from baseline. In patients with pulmonary symptoms (e.g., wheezing, bronchospasm, breathing difficulties, persistent or recurring cough), consider more frequent monitoring of pulmonary function. If symptoms persist, discontinue TI.

Lung cancer: In clinical trials, lung cancer (2 cases in 2750 patient-years of exposure) was reported in the TI group versus none in the comparators (0 cases in 2169 patient-years of exposure). A prior history of heavy tobacco use was identified as a risk factor in both cases. Two additional cases of lung cancer (both squamous cell) occurred in non-smokers exposed to TI and were reported after trial completion. Technosphere insulin should not be used in patients with active lung cancer. Consider the risk versus benefits of using TI in patients with a prior history of lung cancer or in patients at risk for lung cancer.

Diabetic ketoacidosis: In the type 1 diabetes clinical trials, DKA was more commonly reported in the TI group (n=13; 0.43%) than in the comparator groups (n=3; 0.14%). In patients at risk for DKA (e.g., during acute illness or infection), the frequency of glucose monitoring should be increased and injectable insulin should be considered.

As with other insulin products, there is a risk for hypersensitivity reactions, hypoglycemia, hypokalemia, and fluid retention/heart failure with concomitant thiazolidinedione use

Risk Evaluation

Sentinel event advisories (Sources: ISMP, FDA, TJC)

! **High alert medication:** The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Look-alike/sound-alike (LASA) error potentials

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Table 13: LASA

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Afrezza	None	None	None	Aftera Alfenta Amitiza

Drug Interactions

Same as those reported for injectable insulin (refer to product package insert)

Special Populations

Pregnancy: Category C

TI has not been studied in pregnant women and should not be used during pregnancy unless the potential benefits justify the potential risk to the fetus. In pregnant rats given Technosphere carrier particles (vehicle without insulin) subcutaneously during organogenesis in doses of up to 100mg/kg/day (14-21x human exposure resulting from the maximum daily dose of 99mg), no major malformations were noted. When given from gestation day 7 through lactation day 20, decreased epididymis and testes weight (no decrease in fertility), and impaired learning was observed in pups at ≥30mg/g/day (equivalent to 6x human exposure at maximum daily dose).

Adverse maternal effects (not described in package insert) were observed in pregnant rabbits given Technosphere carrier particles subcutaneously during organogenesis in doses of up to 100mg/kg/day including those dose groups with exposure equal to human exposure resulting from administration of the maximal daily dose.

Lactation: TI has not been studied in lactating women. In a rat study, the carrier particle was excreted in milk at approximately 10% of maternal exposure levels. It is highly likely that insulin and the carrier is excreted in human milk. A decision should be made to suspend use of TI or discontinue nursing.

Geriatric Patients: In the clinical trials, 381 patients were ≥ 65 years old; among these, 20 patients were ≥75 years old. No differences in safety and efficacy were noted between older and younger patients.

Renal or Hepatic Impairment: The pharmacokinetics of TI has not been studied in patients with impaired renal or impaired hepatic function. More frequent glucose monitoring and dosage adjustment may be needed in these patients.

Conclusions

The addition of TI to basal insulin was found to be non-inferior to addition of aspart; however, the improvement in A1C was numerically greater with aspart than TI in patients with type 1 diabetes. TI was found to be superior to placebo when added to oral hypoglycemic agents in patients with type 2 diabetes.

There are several safety concerns with TI, including long-term consequences on pulmonary function, risk for lung cancer, and risk of diabetic ketoacidosis in patients with type 1 diabetes.

Due to limited efficacy and potential for serious adverse reactions, the use of TI should at a minimum be restricted to patients with no history of pulmonary disease (e.g., COPD, asthma), are non-smokers for at least 6-months, and have no current or past history of lung cancer or who are not at risk for lung cancer, and who are unable to use injectable insulin.

Patients with T1DM will still require injectable basal insulin. Those with T2DM are usually started on basal insulin + oral agents. The addition of mealtime insulin is typically reserved as a later option. However, in T2DM there are data showing that patients can be managed with injectable mealtime insulin + oral agents. Therefore, for the T2DM patient who is truly averse to needles, inhaled insulin can be an option.

For patients requiring basal insulin, TI can reduce the number of injections necessary. This may be an option for those with insulin-related adverse skin reactions or those working in environments that do not allow needles.

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Appendix 1: Pivotal Trial in Type 1 Diabetes

Study	Eligibility	Dosing	Demographics/Baseline Values	Results
Study 171 24 weeks R, OL, forced titration N=518	**Inclusion:** ≥18 years old T1DM ≥12 months BMI ≤38kg/m2 Stable basal/bolus insulin dose ≥ 3 months with FPG consistently <220mg/dL A1C ≥7.5 and ≤10% Fasting C-peptide≤0.3 pmol/mL Nonsmoker for preceding 6 months Met PFT cutoffs based on NHANES III **Exclusion:** Total daily insulin dose ≥2IU/kg/d; Insulin pump use within 3 months of screening; Prior use of pramlintide, OADs within 6 months; ≥2 unexplained severe hypoglycemic episodes within 3 months of screening; Any hosp or ER visit due to poor DM control within 6 months of screening; Severe DM complications; Allergy or hypersensitivity to insulin; Other conditions that affect A1C measurement (e.g., blood transfusion, hemoglobinopathies); History of asthma, COPD, or other clinically important pulmonary disease; Any significant finding on screening CXR or labs; Active respiratory infection within 12 weeks of screening; Pregnant, lactating, planning pregnancy, or inadequate birth control	4-week basal insulin optimization. All patients put on prandial aspart After randomization, 12 week prandial insulin optimization with continued basal titration if needed 12 week stable dose phase. Insulin can be adjusted only for safety reasons or acute infection, etc. **TI Gen-2+ basal insulin (n=174)** **TI MedTone + basal insulin (n=174)** **Aspart + basal insulin (n=170)** TI Gen-2: 10U TI~ 4units aspart TI MedTone: 15U TI ~4units aspart Doses of insulin titrated according to algorithm. Titration for TI based on 90-min post-prandial BG values; titration for aspart based on pre-meal BG of the next meal Patients in the TI arms were allowed supplemental insulin	Values for TI Gen-2; TI MedTone; and aspart respectively Age (yrs): 37, 40; 39 Male (%): 44.3; 46.2; 43.3 White (%): 94.3; 96; 97.7 Duration of DM (yrs): 16; 17.7; 16.7 Weight (kg): 75.7; 76.8; 72.6 BMI (kg/m2): 26; 26.2; 25.4 A1C (%): 8.0; 8.0; 7.9 FPG (mg/dL): 155; 143.9; 151.6 Glargine/Determir/NPH (%): 70/15/15	

	TI Gen-2	TI MedTone	Aspart
Completed trial (%)	74.7	79.3	88.8
d/c due to AE (%)	9.2	5.2	0
A1C (%)	-0.21		-0.4
A1C≤7% (%)	18.3		30.7
Basal/prandial insulin dose (U)	32/115.4	137.7	26/25.9
Δ in basal/ prandial dose (U)	4/30.7	NS /20.2	1/1.6
FPG (mg/dL)	-25.3	NS	10.2
Weight (kg)	-0.39		0.93

Appendix 2: Pivotal Trial in Type 2 Diabetes

Study 175 R, DB, PC 24 weeks N=353	**Inclusion:** ≥18 years old T2DM ≥12 months BMI ≤45kg/m2 A1C ≥7.5 and ≤10% Treatment with optimal doses of metformin alone or ≥2 OADs on stable dose for ≥ 3 months No prior use of insulin (excluding, during acute illness, gestational , or at initial dx) Nonsmoker for preceding 6 months Met PFT cutoffs based on NHANES III **Exclusion:** Tx with GLP-1 analogs, TZDs, or weight loss drugs within 3 months of screening; ≥2 unexplained severe hypoglycemic episodes within 3 months of screening; Any hosp or ER visit due to poor DM control within 6 months of screening; Severe DM complications; History of asthma, COPD, or other clinically important pulmonary disease; Any significant finding on screening CXR or labs; Use of meds for asthma, COPD or any other chronic respiratory condition; Renal disease or renal dysfunction; Significant CV dysfunction or history within 12 months of screening; Allergy or hypersensitivity to insulin or meds used in study; Active respiratory infection within 30 days of screening; Any history of lung neoplasms; Major organ system diseases including cancer (other than excised skin basal cell) within past 5 years; Women of childbearing potential not using adequate contraception	6-week run-in with current OADs After randomization, 12 week prandial insulin optimization; OADs kept unchanged 12 week stable dose phase. Insulin can be adjusted only for safety reasons or acute infection, etc. Open-label rescue with glargine for those on ≥2 OADs and glimepiride for those on metformin only **TI Gen-2+ OAD (n=177)** **PBO+ OAD (n=176)** Insulin dosing similar to study 171	Values for TI Gen-2; and PBO respectively Age (yrs): 56.7; 56.7 Male (%): 46.3; 42 White (%): 85.3; 88.1 Duration of DM (yrs): 9.7; 9.2 Weight (kg): 90.2; 90.8 BMI (kg/m2): 31.8; 32.4 A1C (%): 8.3; 8.4 FPG (mg/dL): 179.1; 177.2 Metformin only (%): 23.7; 22.7 Metformin + SU (%):64.4; 65.3 Metformin + DPP-4 inhibitor (%): 5.1; 5.1	

	TI Gen-2	**PBO**
Completed trial (%)	84.7	79
d/c due to AE (%)	4.0	5.1
A1C (%)	-0.82	-0.42
% A1C ≤7%	32.2	15.3
FPG (mg/dL	-11.2	-3.8
Weight (kg)	0.49	-1.13
Rescue (%)	6.8	9.7
Daily dose (U)	92.3	128